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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 90/07942
A61M 1/00, 5/168	A1	(43) International Publication Date:	26 July 1990 (26.07.90)

(21) International Application Number: PCT/DK90/00019

(22) International Filing Date: 19 January 1990 (19.01.90)

(30) Priority data:
P-277308 20 January 1989 (20.01.89) PL

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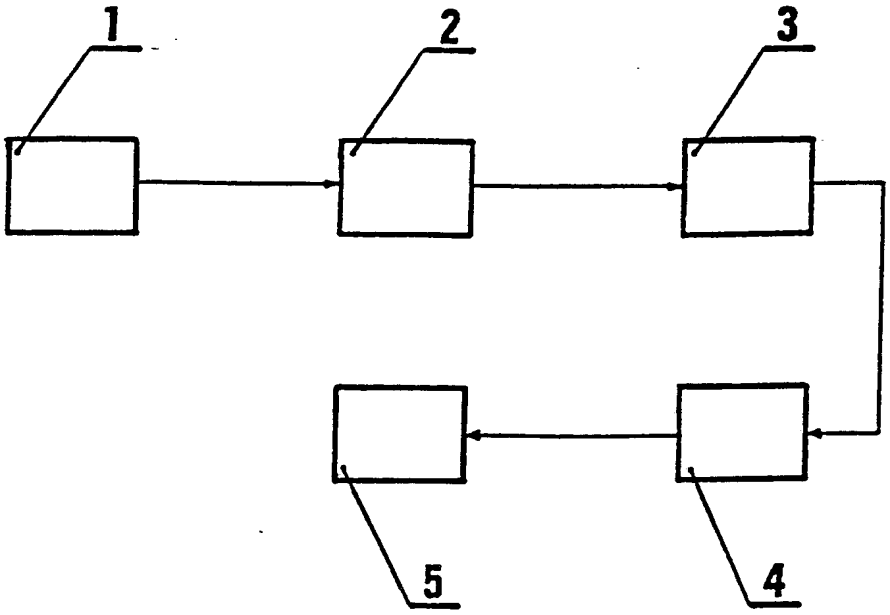
(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

(54) Title: A METHOD OF CONTINUOUS MONITORING OF THE OPERATION OF A DELIVERY SYSTEM, A DEVICE FOR CARRYING OUT THIS METHOD, AND THE USE OF THIS DEVICE



(57) Abstract

A method of continuous monitoring of a delivery system consisting of a volumetric pump (1), an infusion control unit, an electronic measurement unit and an outlet catheter provided with a measuring element, and a device therefor. The method is distinguished by the fact that after every single cycle of the pump the actual pressure and/or the volume of delivery is measured, preferably continuously, in the catheter by measuring the amplitude of the electric signal coming from the measuring element (1) and depending on the pressure and/or the volume of the delivery of the pump and then this measured signal is compared to preset reference values, e.g. in an analyzing system (5). The delivery systems are preferably for insulin administration when treating type-I diabetes and also for analytical laboratories, the chemical and pharmaceutical industries and the like.

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A METHOD OF CONTINUOUS MONITORING OF THE OPERATION OF A DELIVERY SYSTEM, A DEVICE FOR CARRYING OUT THIS METHOD, AND THE USE OF THIS DEVICE.

The present invention relates to a method of continuous monitoring of the operation of a delivery system, in particular for use in insulin administration in the treatment of type-I diabetes, a device for carrying out this method, and the use of this device.

Delivery systems including the device of the present invention are suitable for use not only for medical treatment purposes but it may as well be used as a batch feeder in analytical laboratories, in the chemical and pharmaceutical industries and so on.

There exists a number of different constructional solutions of problems of portable and implantable insulin delivery systems. For instance, a system may consist of: A power supply unit, a drug reservoir, a control system, a volumetric pump with a measuring element and measurement system.

The insulin delivery system usually enables insulin infusion in two forms: (1) the basic infusions aimed to cover the daily requirement of insulin of the body and (2) additional or supplementary infusions meant to compensate the meals - i. e. the bolus infusions - or adjusting the volume of infusion according to increased physical activity or to an increased demand as caused by the so-called dawn phenomenon (The dawn phenomenon is the blood glucose rise taking place between 3 a. m. and 8 a. m. in some individuals.).

Safe operation of an insulin delivery system is a fundamental requirement as a malfunction of a device causing either an overdose of the hormone or a lack of infusion of the hormone constitutes a serious hazard to the life of the patient.

In order to minimize the risk caused by the malfunction in two examples of the best solutions until now, viz. the American delivery systems Betatron I and II (manufactured by Cardiac Pacemakers Inc.), the following alarm states are signalled: Supply voltage drop, empty drug reservoir, blockage of the outlet catheter, microcomputer break-down, failure of the internal memory of the system, a too high frequency of the pump operation, motor break-down, dose of insulin in excess of the established daily dose of insulin and erroneous initial data input (improper programming of the infusion). The Betatron I and II delivery systems are described in some detail in Health Devices, November 1987, "Ambulatory Insulin Infusion Pumps", pp. 351-376 (in which nine ambulatory insulin infusion pumps are evaluated).

In another construction, viz. MRS-1 (manufactured by Disetronic AG/Ltd.) the following features are controlled: Electronic systems, supply battery, drug level in the reservoir, outlet catheter patency and excess doses of insulin administered in the form of boluses.

In the solutions mentioned above alarm states such as empty drug reservoir, a too high frequency of the operation of the pump or a dose of insulin in excess of the daily allowable insulin dose are determined by counting control impulses fed to the pump. Hence, such a monitoring method provides merely an indirect monitoring of the correctness of insulin infusion. This is also true of other alarm

states. For instance, monitoring of the operation of the pump or of the supply battery is carried out by measuring the mechanical movement and by measuring the supply voltage level respectively.

Another issue or problem is connected with the monitoring of the threshold pressure in the outlet catheter of insulin delivery systems (monitoring with a view to "catheter plugging"). A solution to this issue or problem as developed by Siemens is described in: K. Prestele and M. Frentzki, "State of Development of Program-Controlled Implantable Insulin Delivery Systems" in "Artifcial Systems for Insulin Delivery" edited by P. Brunetti et al., 1983, Raven Press, New York, pp. 141-153, in particular pp. 149-150. According to this method the pressure measurement is performed as an indirect non-quantitative check of the insulin flow through the pump outlet. In the discussed solution the system for the measurement of the pressure consists of a non-conducting cylinder having a diameter equal to the inner diameter of the catheter, two electrodes and a unit for measuring the conductivity in the circuit: Electrode - catheter section containing the cylinder - electrode. Under conditions of normal operation of the pump the overpressure generated causes an increase of both the diameter of the catheter and of the flow of the insulin (which is a conductor) around the cylinder. A blockage of the catheter produces a much stronger signal than the signal received during proper operation. If the pressure threshold value is exceeded by 1 bar the alarm is switched on.

The above examples of the best solutions until now of the problems of checking the proper operation of insulin delivery systems control or monitor the operation of particu-

lar units or elements of the systems in ways that allow only indirect monitoring of the correctness of the insulin infusion. The control or monitoring of the number of revolutions of the motor per unit of time or the check of sequences of impulses fed to the pump can by no means lead to a determination of whether the insulin infusion into the body of a patient is proper since there can always be a broken catheter or the pump can be feeding air instead of the drug and so on.

The above mentioned examples have one thing in common: They are all examples of "open-loop" methods of continuous monitoring of the operation of portable insulin delivery systems, pumps for short, and/or "open-loop" type control or monitoring devices for use in carrying out such methods.

Having regard to the above mentioned prior art, and the problems mentioned above, it is the object of the present invention to provide a method of continuous monitoring of a delivery system comprising a volumetric pump, an infusion control unit, an electronic measuring unit and an outlet catheter provided with a pressure sensor in the following referred to as a sensor, and by means of which method at least some of the problems mentioned above will be solved and a device for carrying out this method and by means of which device at least some of the problems mentioned above will be solved.

The stated object of the present invention is achieved by a method, characterized in that during every single cycle of the pump the actual pressure of delivery is measured, preferably continuously, in the catheter.

It has been found - as mentioned below in the description of how the method of the present invention works, this description being given in relation to the drawing - that between the amplitude of the measurement signal - calculated as the difference between the peak value and zero level - on one hand and the pressure and/or the volume of a single pump delivery on the other hand there exists a dependence of some sort which dependence of some sort may be a linear dependence.

Through the control or monitoring of the proper value of the electric signal amplitude from the measuring element or sensor every single delivery of the pump is monitored.

The signal from the measuring element is used simultaneously for monitoring the resistance to the flow of the liquid from the drug reservoir to the pump and from the pump to the patient as well as for checking the supply voltage. This is possible thanks to changes in the signal amplitude occuring whenever any of the above parameters change their value.

Compared to the prior art this is worthy of note since it means that the method of the present invention can be a method of the "closed-loop" type in contrast to the methods of the prior art mentioned above that are of the "open-loop" type.

It is further worthy of note that in turn this means that in the method of the present invention there is provided a feedback that can be used to control the insulin infusions.

The method of monitoring of the present invention is not

related to the performance of any particular element of one or another insulin delivery system but solely to the actual efficiency of the insulin delivery system as measured in the catheter.

It is an advantage in connection with the method of the present invention that the actual delivery of the pump is measured at the outlet of the catheter by measuring the amplitude of the electric signal coming from the measuring element or sensor which signal depends on the pressure and/or the volume of the delivery of the pump and which signal is then compared to preset reference values.

It is another advantage in connection with the method of the present invention that the signal from the measuring element or sensor is transmitted via a matching system to a measurement system and also that the measurement results obtained in the measurement system are transmitted to an analog-to-digital converter and from this analog-to-digital converter to an analysing system before being analysed in this analysing system.

The stated object of the present invention is further achieved by a device that comprises a measuring element or sensor placed in the catheter.

It has been found that between the amplitude of the measurement signal - calculated as the difference between the peak value and zero level - on one hand and the pressure and/or the volume of a single pump delivery on the other hand there exists a dependence of some sort which dependence of some sort may be a linear dependence.

Through the control or monitoring of the proper value of

the electric signal amplitude from the measurement element or sensor every single delivery of the pump is monitored.

The signal from the measuring element is used simultaneously for monitoring the resistance to the liquid flow at drug reservoir to pump and pump to patient as well as for checking the supply voltage. This is possible thanks to changes in the signal amplitude occuring whenever any of the above parameters change their value.

It is further worthy of note that in turn this means that by means of the device of the present invention there is provided a means for feedback that can be used to control the insulin infusions.

The device of the present invention for continuous monitoring of a delivery system consisting of a volumetric pump, an infusion control unit, an electronic measurement unit and an outlet catheter provided with a measuring element and for use in carrying out the method of the present invention is not related to any particular element of one or another insulin delivery system but solely to the actual insulin delivery system comprising a measuring element in the catheter.

It is an advantage in connection with the device of the present invention that the device comprises a measuring element or sensor placed in the catheter and a system for comparing the signal coming from the measurement element or sensor to preset reference values.

It is another advantage in connection with the device of the present invention that the device comprises a measuring element or sensor placed in the catheter, a

matching system, a measurement system, an analog-to-digital converter and an analysing system.

Below the invention will be explained in some detail while having reference to an example of an embodiment of the method of the present invention in which the example of an embodiment of the device of the the present invention shown in the drawing is being utilized. It should be noted that this embodiment of the method of the present invention and that this embodiment of the device of the present invention are given solely as examples and should in no way be considered as limiting the invention in one or more respects.

The drawing shows a block diagram of a delivery system having a volumetric pump and controlled by the delivery of the pump.

In the drawing a measuring element or sensor is provided in the catheter. The signal from this measuring element 1 or sensor 1 is transmitted via a matching system 2 to a measurement system 3. The measurement results obtained in 3 are transmitted to an analog-to-digital converter 4 before being analysed in a system 5.

When the embodiment of the method of the present invention illustrated in the drawing is being used while utilizing the embodiment of the device of the present invention illustrated in the drawing displacement of the fluid by the pump causes the occurence of an overpressure in the pump section which causes the measuring element 1 or sensor 1 to give the signal, the amplitude of which depends on the pressure of the pump delivery. The overpressure decays when the single cycle of the pump work is

completed. The courses of pressure measured by the measuring element 1 in the intervals between the consecutive cycles of the operation of the pump as well as during each cycle of the operation of the pump are converted to electric analog signals. These signals are transmitted via the matching system 2 to the measurement system 3 where the zero level of the signal coming from the sensor 1 (pump on idle) as well as its peak value (pump operates) are measured. The measured parameters are transmitted to the analog-to-digital converter 4 and are next analysed in the system 5.

It has been found that between the amplitude of the measurement signal - calculated as the difference between the peak value and zero level - on one hand and the volume of a single pump delivery on the other hand there exists a dependence of some sort which dependence of some sort may be a linear dependence. Therefore in the discussed solution of the problems of delivery systems the continuous quantitative control or monitoring of the actual delivery of the pump is carried out. Monitoring of the delivery operation of the system consists in continuous comparison of the measured values to the reference values recorded (1) in the memory of the system for comparing the signal coming from the measuring element or sensor to preset reference values or more specifically (2) in the memory of the analysing system 5 and in - if there occurs a discrepency - setting on the alarm.

The measurement signal generated by the measuring element also works as a very sensitive indicator of several malfunctions that may occur during the operation of the delivery system. This concerns: Supply voltage drop, positive or negative external pressure influence, outlet ca-

theter blockage, breakage of the catheter or disconnection of the catheter from the patient, blockage of the connector between the drug reservoir and the pump as well as appearance of an air bubble in the pump.

The occurence of any of the disturbances metioned above causes a decrease or increase in the magnitude of the signal - a drop or rise of the signal - coming from the sensor 1. Consequently, passing the upper or lower values of the settled or preset limits for amplitude, peak value or zero level switches the device to the alarm states.

An example of the schematic description of the decisive signal changes is given in the table to follow.

TABLE, PART ONE

Disturbances	Symptoms caused by the disturbances	Possible alarm states
Battery voltage drop	↓ (Peak value gradual drop)	I
Air bubble inside pump mechanism	↓ (Peak value rapid drop)	II
Blockage of the connector between reservoir and pump	↓ (Peak value rapidly accelerating drop)	II
Increase in the stroke volume	↑ (Peak value rapid rise)	III
Decrease in the stroke volume	↓ (Peak value rapid drop)	I
Influence of an external negative hydrostatic pressure	↓ (Zero level rapid drop)	IV
Influence of an external positive hydrostatic pressure	↑ (Zero level rapid rise)	V

TABLE, PART TWO

Disturbances	Symptoms caused by the disturbances	Possible alarm states
Blockage of the catheter	↑ (zero level rapidly increasing rise)	VI
Catheter cracks	↑ (Zero level rapid rise)	V
Disconnection of the catheter from the body	↑ (Zero level rapid rise)	V

↑ ↓ - direction of changes

The alarm states indicated by roman numerals are not exclusive.

The occurence of any of the disturbances mentioned above changing the signal from the measuring element, thus in the case of supply battery voltage drop, change of a positive external pressure, blockage of the outlet catheter or of the connector between the drug reservoir and the pump or an air bubble in the liquid - causes a rapid drop of the amplitude of the signal coming from the sensor 1 or - in the case of change in the negative external pressure, breakage of the catheter or the disconnection of the catheter from the patient - its rise. Consequently passing the upper or lower values of the settled or preset limit switches the device into one or more of the alarm states.

Thus, the measured signal coming from the sensor 1 can be utilized for simultaneous monitoring of the operation of the pump and of the patency of the junctions from drug reservoir to the pump and from the pump to the patient as well as for checking the supply voltage of the system.

Although the method and the device and the use according to the invention were developed primarily with a view to the administration of insulin to diabetic patients, the method and the device will also be useful in connection with the administration of other dissolved drugs which advantageously can be administered over a prolonged period of time. Examples of such drugs are heparin, oxytocin, human growth hormone and cancer chemotherapeutics.

What has been indicated in the specification in a concrete or specific way relating to the present invention is given as examples only and should in no way be considered as limiting - in one or more respects - to the scope of the present invention which scope is layed down solely by the appended claims as many a modification, change or replace-

ment may be made without passing the limits of the scope of the present invention wholly or in part or without departing from the spirit or the idea of the present invention wholly or in part.

C L A I M S

1. A method of continuous monitoring of a delivery system, in particular for use in insulin administration, comprising a volumetric pump, an infusion control unit, an electronic measuring unit and an outlet catheter provided with a measuring element, characterized in that during every single cycle of the pump the actual pressure of delivery is measured, preferably continuously, in the catheter.

2. A method according to claim 1, characterized in that in connection with every single cycle of the pump the signal from the measuring element is used to calculate the volume of the liquid delivered by the pump during the operation.

3. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following sources of error: 1) Supply voltage and 2) Decrease in stroke volume (Alarm State I).

4. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following sources of error: 1) Air bubble inside pump and 2) Blockage of the connector between reservoir and pump (Alarm State II).

5. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following source of error: Increase in the stroke volume (Alarm State III).

6. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following source of error: Influence of an external negative hydrostatic pressure (Alarm State IV).

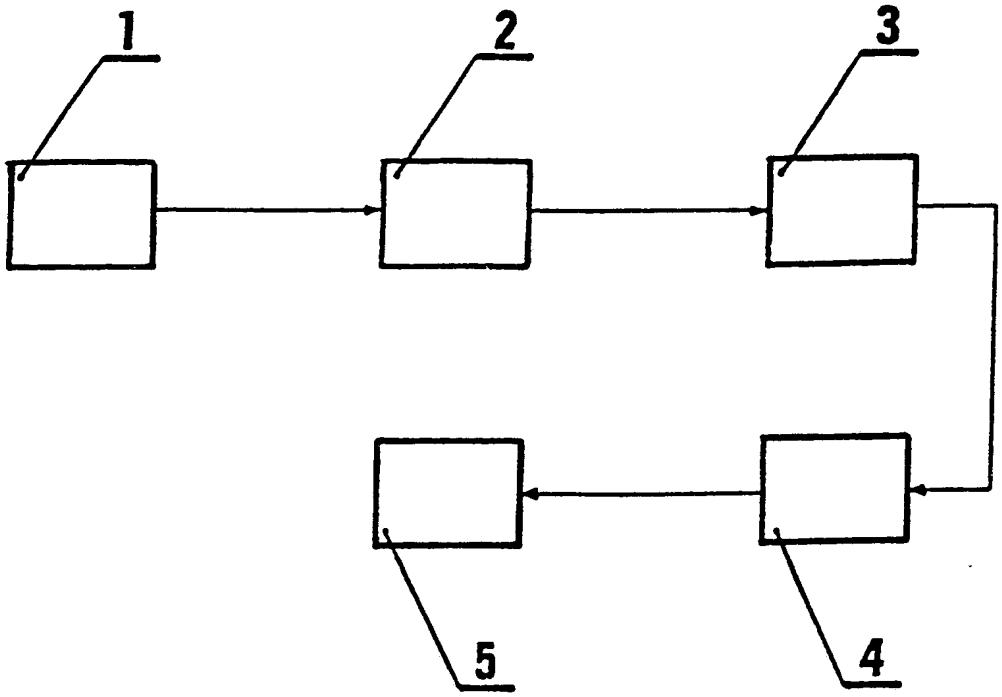
7. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following sources of error: 1) Influence of an external positive hydrostatic pressure, 2) Catheter broken and 3) Catheter disconnected from the body of the patient (Alarm State V).

8. A method according to any of the preceding claims, characterized in that the signal from the measuring element is used to check whether the state of the device is normal with respect to the following source of error: Blockage of the catheter between the measuring element and the outlet (Alarm State VI).

9. A device for continuous monitoring of a delivery system consisting of a volumetric pump, an infusion control unit, an electronic measurement unit and an outlet catheter and for use in carrying out the method according to claims 1 and 8, characterized in that the device comprises a measuring element (1) or sensor (1) placed in the catheter.

10. A device according to claim 9 for continuous monitoring of a delivery system consisting of a volumetric pump, an infusion control unit, an electronic measurement

unit and an outlet catheter, characterized in that the device comprises a measuring element (1) or sensor (1) placed at the outlet of the catheter and a system for comparing the signal coming from the measuring element (1) or sensor (1) to preset reference values.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INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 90/00019

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 M 1/00, 5/168

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System [8]	Classification Symbols
IPC5	A 61 M 1/00, 5/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [9]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A2, 0296124 (FRANTZ MEDICAL DEVELOPMENT LTD.) 21 December 1988, see column 6, line 16 - line 28 --	1-10
Y	EP, A2, 0291727 (ABBOTT LABORATORIES) 23 November 1988, see column 6, line 39 - column 7, line 48 --	1
Y	WO, A1, 84/01719 (THE JOHNS HOPKINS UNIVERSITY) 10 May 1984, see claims 1-26 --	1-10
A	US, A, 4762518 (STEPHEN J. KREINICK) 9 August 1988, see the whole document --	1-10

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th April 1990	1990 -04- 24
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Inger Löfgren

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A2, 0040592 (RODLER, HANS) 25 November 1981, see the whole document --	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 90/00019

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

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		US-A-	4845487	89-07-04
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		US-A-	4457751	84-07-03